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Application No.	PCT/IE99/00038
Date of Filing	7 May 1999
Applicant	SALVIAC LIMITED, an Irish company of 39-40 Upper Mount Street, Dublin 2, Ireland.

Dated this 17 day of August 2001.

An officer authorised by the
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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

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PCT/IE 99/00038

International Application No.

7 MAY 1999

International Filing Date (07.05.99)

IRISH PATENTS OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum) SALV14/C/WO

Box No. I TITLE OF INVENTION

"Biostability of Polymeric Structures"

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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☐ This person is also inventor.

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State *(that is, country)* of nationality: IE

State *(that is, country)* of residence: IE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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This person is:

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☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IE

State *(that is, country)* of residence: IE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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This person is:
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- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

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This person is applicant for the purposes of:
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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CANNON, Ann Marie
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This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IE

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- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

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This person is:
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See Notes to the request form

PCT/IE 99/00038

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes. at least one must be marked)*:

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
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National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

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- ☒ DE Germany ..and utility model.....
- ☒ DK Denmark ..and utility model.....
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Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ ZA South Africa .....
- ☒ AE United Arab Emerates .....
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Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

PCT/IE 99/00030

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	4
description (excluding sequence listing part)	:	14
claims	:	8
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	27

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: 39802, 40018
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

John O'Brien

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1. Date of actual receipt of the purported international application: 07 MAY 1999 (07.05.99)
2. Drawings: ☐ received: ☒ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA / EP
6. ☐ Transmittal of search copy delayed until search fee is paid.

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Date of receipt of the record copy by the International Bureau:

"BIOSTABILITY OF POLYMERIC STRUCTURES"

This invention relates to biostable biocompatible polymeric structures suitable for long term implantation within a living human body and as a suitable substratum for cell growth technologies.

Background of the Invention

Extensive investigations have been undertaken over many years to find materials that will be biologically and chemically stable towards body fluids and body tissue. This area of research has become increasingly important with the development of various objects and articles which can be implanted into a living body, such as pacemaker leads, vascular grafts, mammary prostheses, pacemaker bodies, probes, catheters and the like. Polyurethanes have become crucial to many of these devices.

Flexible polyurethane foams have been manufactured for more than thirty years from polyisocyanates and polymeric polyols. They have been used in the production of elastomers, flexible and rigid foams, coatings, adhesives and many other products in the industrial sector. The most commonly used polyisocyanate has been TDI (Toluene Diisocyanate) but in recent years this has been replaced with MDI (Diphenylmethane Diisocyanates). Isocyanate polyurethane prepolymers obtained by reacting a stoichiometric excess of a polyisocyanate with an organic polyol are well known in the field of polyurethanes.

The production of foamed materials based on polyurethane and other polymer systems derived from organic polysiloxanes in industrial applications is also well established. The formulation and processing conditions used during manufacture affects the properties of the foam product. They can vary in texture from soft flexible foams used in cushioning applications to hard rigid materials used as

insulating or structural materials. The density and strength of the material can also be affected by the formulation.

While there are some polymeric materials available for use in medical implant technologies there is a need for an improved technology for producing polymeric materials with enhanced biostability and biocompatibility.

Statements of Invention

According to the invention there is provided a method for manufacturing a biostable biocompatible polymeric material comprising the step of forming a three dimensional cross linked structure of the polymeric material and treating the structure to remove impurities.

In a particularly preferred embodiment of the invention the structure is treated by solvent extraction.

Ideally the solubility parameter of the solvent extraction system is selected for compatibility with the solubility parameter of the polymeric material or its phases. Preferably the solubility parameter of the solvent extraction system is within $\pm$ 8 $MPa^{\frac{1}{2}}$ of the solubility parameter of the polymer or its phases.

In a preferred embodiment of the invention the method includes the step of removing residual solvent from the structure, after solvent extraction. Preferably residual solvent is removed by treatment with water.

The biostable biocompatible material may for example be a polyether polyurethane or a polycarbonate urethane or polycarbonate urethane urea or a polydimethylsiloxane urethane urea.

In one case the material is in the form of a medical implant. The implant may be a septal defect occluder, a vessel occluder, a vessel defect occluder, a mammary prosthesis, a muscle bulking agent, a gynecological implant or an embolic filter.

The material may be in the form of a substratum for tissue and/or cell growth.

Ideally the material forms a cell matrix for cell growth technologies, tissue repair and in drug delivery applications.

In the case of a biostable polyether polyurethane article the article may be formed from an organic diisocyanate, a polyether polyol, a chain extender and a blowing agent.

The blowing agent is preferably water.

The density of the article is preferably less than 1200kg/m^3, ideally less than 200kg/m^3.

The ratios of the reaction components are selected to promote the formation of a three dimensional porous molecular structure of polyether urethane biomaterial.

The article may be processed by a metering and mixing process, wherein the chemical components are aggressively mixed and dispensed into a vessel and chain extension and blowing reactions occur substantially simultaneously.

Typically the article is processed by a reactive moulding process, wherein the chemical components are mixed and dispensed into a vessel wherein chain extension occurs.

The article may be processed in two stages, a first stage involving a reaction process in which the number of isocyanate linkages in the reaction vessel is approximately equal to the number of active hydrogens in the vessel.

The article may also be processed by a reactive blowing process, in which the chemical components are aggressively mixed and dispensed substantially continuously and expand and chain extend substantially simultaneously to form a continuous block of foam which is subsequently cut or machined into a desired geometry.

The density of the article is preferably controlled by controlling the pressure in the reaction vessel.

Preferably the biostable polyether polyurethane article has a pore size of from 10 microns to 900 microns. Ideally the biostable polyether polyurethane article according to claim 25 having a pore size of between 35 microns to 200 microns.

In one aspect the invention provides a biostable polyether polyurethane wherein the urea linkages are derived from a water isocyanate reaction present in the hard segment phase. Preferably the percentage of urea linkages in the hard segment phase is greater than 0.5%.

In another aspect the invention provides a biostable polyether polyurethane wherein biuret linkages exist in the hard segment phase.

In a further aspect the invention provides a biostable polyether polyurethane wherein aliphatic linkages exist in the hard segment phase.

Further details of the invention are set out in claims 31 to 53.

Detailed Description

The biostable polyurethane devices of this invention are derived from organic diisocyanates and polyether polyols, polyether copolymer polyols or combinations thereof and are chain extended with either diamine, diol, water or mixtures of the above chain extenders. The reaction step converts the chemical precursors into a 3 dimensional molecular cross-linked structure, simultaneously forming a low density porous material. A 3 dimensional network of this kind is insoluble and intractable. Manufacturing the article by this method produces a material with minimal internal stress, enhancing biostability.

The fact that the polyether biomaterial is a three dimensional structure at a molecular level allows it to be processed aggressively to remove residual chemicals from the process. Low molecular weight chemicals have the potential to leach from the article and result in toxic reactions in living cells. The downstream processing of the article expands the biomaterials volume at a molecular level. This expansion aids in the removal of leachables such as catalyts, oligomers and free monomers. The solvent extraction process also reduces any internal stresses within the material. The solvent expands the material when it penetrates between the molecular chains. The 3-dimensional cross links provides the materials with molecular memory and prevents the molecular structure being soluble in the solvent. However, the molecular chains in this state can orient themselves into a preferred relaxed conformation, thereby relieving the material of any internal stresses.

This process enhances the material biocompatible for use as an implantable medical device or as a 3 dimensional matrix for use as a cell scaffold in tissue engineering applications. Altering the chemical precursors and the processing conditions of the material may alter the pore size and the density of the material, as required, to meet the requirements of the application.

The biostable polyurethanes of this invention are useful for the manufacture of catheters, vascular grafts, septal occluders, vessel occluders, embolisation devices, mammary prosthesis, pacemaker leads and other such implant, blood contacting devices and as cell scaffolds to support cell growth.

The biostable polyurethanes of this invention are based on organic diisocyanates, polyether copolymer polyols, polyether homopolymers and diol, diamine or water chain extenders and combinations thereof.

The product of this invention has applications in the medical device and tissue engineering sectors, however the material can also be used as a cell scaffold to support cell growth.

This material is suitable for these applications since it was designed such that an aggressive solvent extraction process can be applied to remove potential leachables from the material. Typically it is these leachables that are responsible for cytotoxic responses to polyurethane materials. The solvent extraction system detailed in this invention allows the use of solvents with a solubility parameter similar to that of the polymer, allowing the polymer to swell and the leachables to be removed by the solvent from the material.

Linear polymer systems cannot be subjected to such an aggressive solvent extraction since the use of a solvent with a similar solubility parameter will cause both the polymer and it's leachables to dissolve. It is the 3 dimensional structure of the biomaterial of this invention that permits the use of a solvent of a similar solubility parameter since the 3 dimensional structure of the material gives it inherent molecular memory allowing it to return to it's original configuration.

Swelling the 3 dimensional polymer with similar solvents opens up the structure and allows extraction of chemical species impossible to extract in linear systems by conventional dissimilar solvents.

To manufacture and process linear polymers into required geometries, normally requires the use of additives and catalysts, which cannot be removed completely by conventional solvent extraction. The 3 dimensional material , detailed in this invention can be laser machined into the required geometries.

Details on the chemistry of the invention are as follows;

The organic diisocyanates are of the general formula:

$R\text{-}(NCO)_n$

R is an aliphatic, aromatic, cycloaliphatic, or an aliphatic-aromatic hydrocarbon entity containing between 4 and 24 carbon atoms and "n" varies between 1.85 and 3. More preferably, R contains between 4 and 13 carbon atoms. Where n is 2, a polymer with a linear molecular structure may be produced. A three dimensional molecular network may be produced where n varies from 1.85 to 3. Ideally n should be between 1.9 and 2.2.

Examples of suitable isocyanates include: p-phenylene diisocyanate, tetramethylene diisocyanate, cyclohexane 1, 2-diisocyanate, m-tetramethylxylene diisocyanate, hexamethylene diisocyanate, 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate, 4,4 -dicyclohexylmethane diisocyanate, 4,4 -dicyclohexylmethane diisocyanate, and mixtures of the above.

More ideally the following isocyanates can be used to manufacture suitable materials; 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate, 4,4 -dicyclohexylmethane diisocyanate, and mixtures of the above.

Even more ideally, the following diisocyanates can be used to manufacture suitable polyurethanes: 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 4,4 -dicyclohexylmethane diisocyanate.

Polyether polyols that may be used include products obtained by the polymerisation of cyclic oxide, for example, ethylene oxide, propylene oxide, butylene oxide, or tetrahydrofuran in the presence of polyfunctional initiators. Suitable initiator compounds contain plurality of active hydrogen atoms including water and polyols, e.g., ethylene glycol, propylene glycol, diethylene glycol, resorcinol, bisphenol A, cyclohexane dimethanol, gylcerol, trimethylolpropane, 1,2,6, - heaxanetriol or pentaerythriol.

Useful polyether polyols include polytetramethylene glycols obtained by the polymerisation of tetrahydrofuran. The polytetramethylene glycols used in this invention having varying molecular weights of between 600 and 3000. Polyols of differing molecular weights can be used together in a single formulation.

The polyether polyurethanes of this invention are based on diol, diamine, alkanolamine, water chain extenders or mixtures of these. Diol chain extenders react with isocyanate to generate urethane linkages. Diamine and water generate urea linkages and alkanol amines can generate both urethane and urea linkages. The use of water as a chain extender in low density, three dimensional biomedical polyurethanes is unusual as with most conventional biomedical polyurethanes water is viewed as an impurity. The water chain extension reactions generate urea linkages in the hard segment and carbon dioxide is given off as a by-product. The presence of significant quantities of urea linkages in the hard segment has the following important effects:

- Polyureas in the hard segment generate significant levels of hydrogen bonding that causes the hard segment to be strong and this adds to the ultimate properties of the material.

- It also promotes phase separation of the hard isocyanate/chain extender phase and the soft polyol phase. Phase separation is beneficial to the elastomeric and biocompatibility properties of the material.
- The presence of significant concentrations of urea linkages in the hard segment make linear polyurethanes difficult to process by thermomechanical techniques.
- The carbon dioxide generated from the water isocyanate reaction series can be used to influence the density of the material by generating a cellular structure.

Polyurethanes with a high concentration of urea linkages in the hard phase tend to be strong elastomers with good flex lives.

The carbon dioxide generated as a by-product of the isocyanate-water-isocyanate reaction series can be employed to generate a cell structure in the material. With the use of a surfactant, the size and porosity of this cell structure can be controlled. The manufacturing control over the pore size of the material has important implications in the application of the article. In cell growth technology the pore sizes can be modified to accommodate cells and modify the cell to surface ratio.

The level of water used in the reaction determines the amount of carbon dioxide generated and the hard segment content of the polymer. The amount of carbon dioxide generated plays an important role in the density of the polyurethane. By this invention, the density can be controlled independently of the hard segment content by controlling the pressure of the reaction/forming chamber. Thus, biostable polyurethanes of this invention can be manufactured with densities ranging from 15kg/m^3 to 1200kg/m^3 virtually independent of the hard segment content. Low density articles used in medical applications are desirable since the wrapping profile of the article is reduced and the delivery device profile is minimised, giving rise to a wider range of applications.

The polymerisation of biostable polyurethanes of this invention involves the reaction of -OH groups from the polyol with -NCO groups from the diisocyanate to form urethane linkages. These chemical groups are reacted in approximately equivalent ratios for the generation of linear polymers and with slight excess for a crosslinked (three-dimensional) molecular structure.

For the generation of biostable foams, water is used as the primary chain extender. Secondary chain extenders may be employed to alter the hard segment content or to alter specific properties. Manufacturing foams of the lowest densities per this invention is carried out by a combination of a water blown reaction, in a depressurised reactive/forming vessel and the incorporation of a physical blowing agent into the formulation. Secondary chain extenders can be either diamine, diol or alkanol amine based and should have a functionality of two or greater. Diol chain extenders are preferred.

Most diols or diamines make suitable chain extenders. Examples of such chain extenders include, ethylene glycol, 1,4 butanediol, diethylene glycol, triethylene glycol, 1,2 propane diol, 1,3 propane diol, 1,5 pentane diol, ethylene diamine, 1,4 diaminobutane, 1,6 diaminohexane, 1,7 diaminoheptane, 1,8 diaminooctane, and 1,5 diaminopentane.

Depending on the specific isocyanate reactive compounds used, the use of catalysts may be preferred or not. Using polyols as isocyanate reactive compounds, it is preferred to use catalysts for urethane formation. Catalysts for polyurethane formation that may be used are compounds, which promote the reaction between isocyanate and hydroxyl groups.
Such catalysts are widely available in the marketplace and include organic and inorganic salts of bismuth, lead, tin, iron, antimony, cadmium, cobalt, aluminum, mercury, zinc, cerium, molybdenum, vanadium, copper, manganese and zirconium, as well as phosphines and tertiary amines.

Tertiary amines are an important class of catalyst in which the nitrogen atom is not directly attached to an aromatic ring. Examples of tertiary amines are: triethylamine, N,N,N',N'-tetramethylenediamine, N-N,N',N'-tetramethyl-1,3-butanediamine, bis-2-dimethylaminoethyl ether, N,N-dimethylcyclohexylamine, N,N-dimethylbenzylamine, N-methylmorpholine, N-ethylmorpholine, 1,4–diazabicyclo-[2.2.2] octane and the like.

Biostable articles of this invention can be chemically prepared via the following methods:

The one shot process in which the diisocyanate, the polyol and the chain extender are mixed and reacted in one step.

The prepolymer method wherein an isocyanate-terminated prepolymer is first prepared and then the system is chain extended. An experienced person knowing the isocyanate content of the isocyanate composition and the functionality and molecular weight of the isocyanate- reactive compound, can calculate the relative amounts of reactants to be delivered to the reaction vessel in order to provide a prepolymer having any desired NCO content.

The quasiprepolymer system wherein some of the polyol is reacted with the isocyanate to generate an isocyanate terminated prepolymer in an excess of isocyanate. The remaining polyol and chain extenders are subsequently added to facilitate chain extension.

Biostable articles of this invention may be processed by any of the following techniques:

- Reactive blow moulding process, wherein the chemical ingredients for this invention are fed though two or three lines to a mixing head where it is aggressively mixed and dispensed into a mould and chain extension and blowing reactions occur simultaneously. This process is suitable for the manufacture of a three dimensional molecular structure and is suited to the manufacture of low density porous and non-porous articles. The shot size

used in this invention is 0.5g to 10g producing a three dimensional low density porous foam.

- Reactive blowing process, wherein the chemical ingredients are aggressively mixed and dispensed in a continuous fashion and expand and chain extend simultaneously to form a continuous block of foam which is subsequently cut or machined into useful shapes. This process is suitable for the manufacture of a three dimensional molecular structure and is suited to the manufacture of low density porous and non-porous articles.

The biostable polyurethane of this invention is solvent extracted to enhance the biocompatibility of the polyurethane article. This process can be applied to all polyurethane materials. The material of this invention has a structure that is three dimensional and crosslinked at a molecular level. This allows for use of more aggressive solvents with similar solubility parameters without destroying the integrity of the material. The process allows any internal stresses to be relieved, enhancing biostability.

Biocompatibility of a material in contact with bodily fluids is a primary function of two variables :

- Surface chemistry of the implant : for polyurethanes it is widely accepted that the surface that displays alternating, well phase separated hydrophobic and hydrophilic domains provides optimum biocompatibility.
- Leachables with the implant : the severity of the inflammation of the surrounding tissue is strongly dependant on the type and quantity of products which can migrate from the implant to the surrounding tissue. Leachables can be removed from the foam via solvent extraction.

Different solvents are available for carrying out this process. The solubility and hydrogen bonding parameters of the solvent will affect the suitability of the solvent. The solubility of polyurethane foams is typically in the region of 17 –28

$MPa^{1/2}$. The solvent system used for the extract system should have a solubility parameter close to in the same range as the foam.

Solvent that may be used are : methylethyl ketone, tetrahydrofuran, dimethylformamide, 1,2 – dichloroethane, n-heptane, diethylether, acetonitrile, propan-2-ol, methanol and combinations of the above.
On immersion of the foam into the chosen solvent system the leachables from the polymer are drawn into the solvent if the leachables are soluble in the solvent system.

If the solubility parameter of the solvent system is close to that of the volume of the polymer will extend and allow extraction of low molecular weight species. It is important to maintain the integrity of the foam during this process. The residual solvent is removed from the structure using a water extraction step. The molecular memory allows it to return to its original configuration.

Cleaning the foam in such a manner removes all leachables and makes the foam suitable for long term implantation in the human body and as a cell scaffold to promote cell growth in tissue engineering applications.

The article may be used as a cell scaffold to provide a substratum to promote the growth of adherent cell lines. Cells may be seeded onto the material, attach to the cell scaffold and replicate in a physiologically suitable environment. The nature of the article provides a large surface: area ratio, to enable cells infiltrate the material. The nature of the 3 dimensional material also allows the diffusion of nutrients and oxygen into the media and the diffusion of waste metabolites and carbon dioxide gas to leach from the three dimensional structure of the article. The cells can also secrete proteins as determined by the genetic make up of the cell.
As a result of the open cell structure of the material, cell – cell interactions can take place forming the basis of tissue formation.

This article has a number of applications in the field of cell growth/tissue engineering not limited to

- The use of the article as an implantable medical device to promote the growth of new tissues.
- The use of the article seeded with a specific cell type, implanted to promote the growth of new tissues.
- The use of the article in *in vitro* cell culture technologies and related applications.

It will be appreciated that the treatment of polymeric structures to remove impurities may be applied to any suitable polymeric material. In particular the invention may be applied to the polycarbonate urethane material described in or co-pending PCT application No IE 98/00091, filed November 9, 1998, the entire contents of which are incorporated herein by reference.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

Claims

1. A method for manufacturing a biostable biocompatible polymeric material comprising the step of forming a three dimensional cross linked structure of the polymeric material and treating the structure to remove impurities.

2. A method as claimed in claim 1 wherein the structure is treated by solvent extraction.

3. A method as claimed in claim 2 wherein the solubility parameter of the solvent extraction system is selected for compatibility with the solubility parameter of the polymeric material or its phases.

4. A method as claimed in claim 3 wherein the solubility parameter of the solvent extraction system is within ± 8 $MPa^{½}$ of the solubility parameter of the polymer or its phases.

5. A method as claimed in any of claims 2 to 5 including the step of removing residual solvent from the structure, after solvent extraction.

6. A method as claimed in claim 5 wherein residual solvent is removed by treatment with water.

7. A biostable biocompatible material whenever prepared by a method as claimed in any of claims 1 to 6.

8. A biostable biocompatible material as claimed in claim 7 wherein the material is a polyether polyurethane.

9. A biostable biocompatible material as claimed in claim 7 wherein the material is a polycarbonate urethane.

10. A biostable biocompatible material as claimed in claim 7 wherein the material is a polycarbonate urethane urea.

11. A biostable biocompatible material as claimed in claim 7 wherein the material is a polydimethylsiloxane urethane urea.

12. A biostable biocompatible material as claimed in any of claims 7 to 11 wherein the material is in the form of a medical implant.

13. A biostable biocompatible material as claimed in claim 12 wherein the implant is a septal defect occluder, a vessel occluder, a vessel defect occluder, a mammary prosthesis, a muscle bulking agent, a gynecological implant or an embolic filter.

14. A biostable biocompatible material as claimed in any of claims 7 to 11 wherein the material is in the form of a substratum for tissue and/or cell growth.

15. A biostable biocompatible material as claimed in claim 14 wherein the material forms a cell matrix for cell growth technologies, tissue repair and in drug delivery applications.

16. A biostable polyether polyurethane article as claimed in any of claims 8 and 12 to 15 formed from an organic diisocyanate, a polyether polyol, a chain extender and a blowing agent.

17. A biostable polyether polyurethane article as claimed in claim 16 wherein the blowing agent is water.

18. A biostable polyether polyurethane article according to claim 16 or 17, wherein the density of the article is less than 1200kg/m^3.

19. A biostable polyether polyurethane article according to claim 16 or 17, wherein the density of the article is less than 200kg/m^3.

20. A biostable polyether polyurethane article according to any of claims 16 to 19 wherein the ratios of the reaction components are selected to promote the formation of a three dimensional porous molecular structure of polyether urethane biomaterial.

21. A biostable polyether polyurethane article according to any of claims 16 to 19 wherein the article is processed by a metering and mixing process, wherein the chemical components are aggressively mixed and dispensed into a vessel and chain extension and blowing reactions occur substantially simultaneously.

22. A biostable polyether polyurethane article according to claim 21 wherein the article is processed by a reactive moulding process, wherein the chemical components are mixed and dispensed into a vessel wherein chain extension occurs.

23. A biostable polyether polyurethane article according to claim 20 wherein the article is processed by a reactive blowing process, in which the chemical components are aggressively mixed and dispensed substantially continuously and expand and chain extend substantially simultaneously to form a continuous block of foam which is subsequently cut or machined into a desired geometry.

24. A biostable polyether polyurethane article in any of claims 20 to 23 wherein the density of the article is controlled by controlling the pressure in the reaction vessel.

25. A biostable polyether polyurethane article as claimed in any of claims 15 to 24 having a pore size of from 10 microns to 900 microns.

26. A biostable polyether polyurethane article according to claim 25 having a pore size of between 35 microns to 200 microns.

27. A biostable polyether polyurethane wherein the urea linkages are derived from a water isocyanate reaction present in the hard segment phase.

28. A biostable polyether polyurethane wherein the percentage of urea linkages in the hard segment phase is greater than 0.5%.

29. A biostable polyether polyurethane wherein biuret linkages exist in the hard segment phase.

30. A biostable polyether polyurethane wherein aliphatic linkages exist in the hard segment phase.

31. A biostable polyether polyurethane article as claimed in any of claims 16 to 30, in which the isocyanate is selected from p-phenylene diisocyanate, tetramethylene diisocyanate, cyclohexane 1, 2-diisocyanate, m-tetramethylxylene diisocyanate, hexamethylene diisocyanate, 2,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, isophorone diisocyanate,, 4,4 -dicyclohexylmethane diisocyanate, 4,4, diphenylmethane diisocyanate, or mixtures thereof, especially with a triisocyanate.

32. A biostable polyether polyurethane article according to claim 31, in which the isocyanate is selected from 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane diisocyanate, 2,4 toluene diisocyanate, 2, 6 toluene diisocyanate, cyclohexane 1,4 diisocyanate, 4,4 -dicyclohexylmethane diisocyanate or mixtures thereof.

33. A biostable polyether polyurethane article according to claim 32 in which the isocyanate is 2,4 diphenylmethane diisocyanate, 4,4 diphenylmethane or 4,4 -dicyclohexylmethane diisocyanate and mixtures thereof.

34. A biostable polyether polyurethane article as claimed in any of claims 15 to 33 wherein said article is formed by the reaction of an aliphatic, aliphatic-alicyclic, aromatic, or aromatic-aliphatic diisocyanate or mixtures of said organic diisocyanate and a polyether polyol having a functionality of 2 or greater.

35. An article as claimed in claim 34 wherein the polyether polyol is of the formula

$$HO - [R_1-O]_n-H$$

where R_1 represents a linear hydrocarbon chain of from 2 to 16 carbon atoms and wherein n has a value greater than 2.

36. A biostable polyether polyurethane article of claim 35 wherein the polyether is a polyalkylene ether wherein the molecular weight is from 300 to 6000 molecular weight units.

37. A biostable polyether polyurethane article as claimed in claim 36 wherein the molecular weight is from 600 to 3000 molecular weight units.

38. A biostable polyether polyurethane article according to claim 36 or 37 wherein the polyol is selected from one or more of polyethylene glycol, polypropylene glycol, polydiethylene-ether glycol or polycaprolactone glycol.

39. A biostable polyether polyurethane article as claimed in claim 36 or 37 wherein the polyether polyols are polytetramethylene ether glycols.

40. A biostable polyether polyurethane article of claim 39 wherein the polytetramethylene ether glycols have a molecular weight of from 150 to 6000 molecular weight units.

41. A biostable polyether polyurethane article of claim 39 wherein the polytetramethylene ether glycols have a molecular weight of from 300 to 3000 molecular weight units.

42. A biostable polyether polyurethane article as claimed in any of claims 15 to 41 formed from a prepolymer composition having an average functionality (n) of from 1.8 to 5.

43. A biostable polyether polyurethane article as claimed in any preceding claim wherein the chain extender is selected from a diol, a diamine, an alkanol amine, water or mixtures thereof.

44. A biostable polyether polyurethane article as claimed in claim 43 wherein the diol is an aliphatic diol having 2 to 10 carbon atoms.

45. A biostable polyether polyurethane article as claimed in claim 43 wherein the diamine is an aliphatic diamine having 2 to 10 carbon atoms.

46. A biostable polyether polyurethane article as claimed in claim 43 wherein the alkanol amine is an aliphatic alkanol amine having from 2 to 10 carbon atoms.

47. A biostable polyether polyurethane article as claimed in claim 43 or 44 wherein the aliphatic diol chain extender is selected from ethylene glycol, 1,4 butanediol, diethylene glycol, triethylene glycol, 1,2 propane diol, 1,3 propane diol, 1,5 pentane diol, isomers or mixtures thereof.

48. A biostable polyether polyurethane article as claimed in claim 43 wherein the aliphatic diamine chain extender is selected from ethylene diamine, 1,4 diaminobutane, 1,6 diaminohexane, 1,7 diaminoheptane, 1,8 diaminooctane, 1,5 diaminopentane, isomers or mixtures thereof.

49. A biostable polyether polyurethane article as claimed in claim 43 wherein the aliphatic alkanol amines chain extender is triethanolamine.

50. A biostable polyether polyurethane article as claimed in any of claims 15 to 49 including a diol, a diamine and/or an alkanol amine as a second chain extender.

51. A biostable polyether polyurethane article according to claim 50 wherein the second chain extender is an aliphatic diol having from 2 to 10 carbon atoms.

52. A biostable polyether polyurethane article according to claim 50 wherein the second chain extender is an aliphatic diamine having 2 to 10 carbon atoms.

53. A biostable polyether polyurethane article according to claim 52 wherein the second chain extender is an aliphatic alkanol amine having from 2 to 10 carbon atoms.

Abstract

A method for manufacturing a biostable biocompatible polymeric material comprises a three dimensional cross linked structure of the polymeric material and treating the structure by solvent extraction to remove impurities. The biostable biocompatible polymeric material is in a form of a medical implant or a substratum for tissue and/or cell growth.